

June 1<sup>st</sup>, 2018

**Physical Therapy and Nerve Gliding Exercises for the Treatment of  
Chemotherapy Induced Peripheral Neuropathy**

**Clinical trials number NCT02239601**

**PROTOCOL**

**METHODS**

**Participants and eligibility**

Stage I-III patients with breast cancer that attended oncology clinics at CancerCare Manitoba were eligible for enrolment if they were receiving standard taxane chemotherapy. Two different chemotherapy regimens were included 1) docetaxel 75mg/m<sup>2</sup> and cyclophosphamide x 4 (TC) or 2) 5-fluorouracil, epirubicin, cyclophosphamide x3, followed by Docetaxel 100mg/m<sup>2</sup> x 3 (FECD)(Jones et al., 2009; Roche et al., 2006; Swain et al., 2013). Participants were approached by a member of the team at their initial oncology visit to advise them of the physical therapy study taking place. If interested, patients signed a consent to contact form. Participants were excluded if they had co-morbid conditions causing peripheral neuropathic symptoms (including previous chemotherapy) or patients not scheduled for regular Taxane therapy. In total, 80 patients were contacted to participate between November 2014 and January 2017. Sixty-one participants were enrolled and 7 withdrew over the course of the study. Reasons for withdrawal included too ill to continue, too busy to continue, or re-diagnosed as stage IV. Data collection was complete by October of 2017 and consisted of 54 participants. Six participants had received neo-adjuvant chemotherapy or chemotherapy that differed from the TC or FECD regimes and were excluded from

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analysis because these regimes substantially affected the timing for surgery, and in some cases, the overall dose of taxane chemotherapy. Forty-eight participants were then included for analysis. Figure 1. Provides a consort diagram of the enrolment process.

## **Protocol**

This was a single blind (blinded assessor) randomized controlled pilot study testing the potential for nerve specific home exercises to improve pain and function post-surgery during and after chemotherapy. Random numbers were drawn to assign either treatment or control. Envelopes containing the assigned group were sealed and the blinded assessor needed only to provide the envelope to the participant after initial consent and assessment. Ethics approval was obtained from both the Health Research Ethics Board (H:2014:281) at the University of Manitoba and the Research Resource Impact Committee (RRIC 2014-031) at CancerCare Manitoba.

Nerve assessments using quantitative sensory testing were administered at the Pain Research Laboratory (PRL), College of Rehabilitation Sciences, University of Manitoba. Quantitative sensory testing (QST) are a variety of non-invasive tests aimed at quantifying sensory perceptions commonly used in research (Boyette-Davis et al., 2013; Hershman et al., 2011; Park et al., 2011; Walk et al., 2009). It is used for sensory detection and pain thresholds for both mechanical and thermal stimuli. The advantages of using QST are that, 'the experimental stimulus, intensity, duration, and modality are controlled; the responses are quantifiable; and, can be compared over time' (Arendt-Nielsen & Yarnitsky, 2009).

## **Outcome Measures**

### Primary Outcome Measures for Physical Therapy Intervention

The primary outcome measures related to function and quality of life and included the Numeric Pain Rating Scale (NPRS), the Disability of the Arm, Shoulder and Hand (DASH), and the Self report version of the Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS).

1) Numeric Pain Rating Scale (NPRS) rated CIPN pain. The NPRS is an 11 point scale (0-10) ranking pain from 0 indicating no pain at all to 10 indicating worst pain imaginable on each assessment visit of the finger tips. This was to specifically identify pain from CIPN. A change score of 2 is reported to be a clinically relevant change.

2) Disability of the Arm, Shoulder and Hand (DASH) is a 30 item participant reported questionnaire commonly used to gauge upper limb function (attached in appendix E). The DASH was chosen because of high test-retest reliability and the responsiveness and construct validity in patients with breast cancer over other quality of life measures (Beaton et al., 2001; Harrington, Michener, Kendig, Miale, & George, 2014). A minimal clinical important difference is a change score of 15.

3) Self report version of Leeds Assessment for Neuropathic Symptoms and Signs (S-LANSS) is a 7 item patient reported questionnaire and was used to confirm the presence of neuropathic pain (Bennett, Smith, Torrance, & Potter, 2005). The score ranges from 0-19 with a score above 12 indicative of neuropathic pain/symptoms. S-LANSS was chosen because of its' specificity and accuracy in a cancer population

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(Hardy, Quinn, Fazekas, Agar, & Currow, 2013; Perez et al., 2015). Participants were requested to answer specifically for the hands, not feet (attached in appendix E).

### Secondary Outcome Measures for Physical Therapy Intervention

Secondary outcomes included vibration sensation assessment as a measure of A $\beta$  function, pain pressure thresholds as a measure of central sensitization, and grip strength as a general measure of function.

1) Vibration analysis testing for perception thresholds are specific to A $\beta$  nerve fibres.

The TSAII Vibration Sensory Analyzer module for the Medoc was used. The pulp of the index finger lightly touches the sensor. The sensor delivers different vibration amplitudes ( $\mu\text{m}$ ). Random, varying vibration thresholds are delivered with the participant responding “yes/no” to sensing the vibration. Vibration perception was selected for its sensitivity and has been suggested to be the first clinical sign of CIPN symptoms and was tested bilaterally (Gutierrez-Gutierrez, Sereno, Miralles, Casado-Saenz, & Gutierrez-Rivas, 2010).

2) Pressure Algometry measured pressure/pain thresholds. It is a hand-held device (Somedic AB, Sweden) and applied perpendicular to the muscles being tested.

Increasing pressure is applied until the participant determines that the sensation has changed from a feeling of pressure to a feeling of pain. The test stops when the participant presses a button, and the force (Kpa) was recorded. The left quadriceps muscle was tested as a measure of central sensitization.

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3) Hand Dynamometry records grip strength in kgs and was used as a measure of function (3 trials). The dominant hand was tested. For our participants, all 48 in analysis were right handed.

### Outcome Measures Assessing Dual Nerve Disorder

QST using the neurosensory analyzer (TSA II, Medoc) for thermal and vibration sensation quantified the differences between surgical and non-surgical side.

1) Thermal detection threshold (warm and cool) and thermal pain thresholds (hot and cold) measured A $\delta$  and C-fibre function. The Neurosensory Analyzer (TSA II, Medoc, Israel) thermode was attached to the volar surface of the index and middle distal phalanx. Temperature was increased or decreased by 0.1-degree Celsius increments until the patient pressed a button indicating temperature detection or thermal pain. The patient is always in control and is never at risk for tissue damage (temperature limits are set to vary only from 0-50 degrees Celsius). Hands were tested bilaterally.

2) Vibration analysis testing from the physical therapy data was used for A $\beta$  nerve fibre function (Vibration Sensory Analyzer module, TSA II).

### **Assessment Visits**

Five visits in total with the research coordinator were required over an average of 8 months at the Pain Research Laboratory (PRL), College of Rehabilitation Sciences, University of Manitoba. The first visit proceeded after the initial oncology visit confirmed

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chemotherapy was required. This primary assessment (visit 1) consisted of completing the informed consent and baseline nerve evaluation including the subjective questionnaires and QST data. Pre-randomized envelopes were sent home with participants that contained which experimental group they were assigned to either physical therapy treatment or standard care. Participants were advised not to disclose their assigned group to the research coordinator in order to maintain blinding. If participants had questions, they were to contact the oncologist or co-investigator involved in the study. Standard care for the control group was to attend nerve re-assessments at the pain research laboratory, but no exercises or appointments with a physical therapist were provided. Instructions only in the treatment group envelope directed participants to arrange 3 sessions at their convenience with the physical therapist prior to the start of chemotherapy.

An estimated nerve re-assessment date for Visit 2 was scheduled for all participants based on their treatment cycles and start date. Visit 3 was post-chemotherapy. Visit 4 was 3 months post-chemotherapy and Visit 5 was the final assessment at 6 months post-chemotherapy. After final evaluation participants could disclose whether they were treatment or control, and they signed a form to receive a \$70 honorarium to cover transportation costs. Patients with residual symptoms allocated to the control group were then offered a physical therapy assessment and tailored home program.

### **Physical Therapy treatment**

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Four visits with a certified hand physical therapist to develop a home exercise and education program were provided to each of the participants in the treatment group prior to their first round of chemotherapy. The three appointments provided upper extremity nerve gliding exercises that were the focus of the daily home program and upper extremity range of motion exercises to restore pre-operative range, if required. Nerve gliding exercises are frequently used exercises to improve neural excursion across joints, improve pain and decrease inflammation (Coppieters & Butler, 2008; Nee, Vicenzino, Jull, Cleland, & Coppieters, 2012; Schmid et al., 2012). Nerve gliding exercises were completed several times daily and required approximately 5-10 minutes of time to complete. Participants were advised to complete these exercises during chemotherapy and after until the symptoms of neuropathy subsided.

Education was provided on how to manage symptoms of neuropathic pain, cold intolerance and hyperalgesia. This included the possibility of using compression gloves, heated mittens, resting splints and desensitization exercises. Education was also provided for hypoesthesia symptoms including safety and protection. Stretching exercises for the neck and upper limb and axillary webbing exercises were provided if appropriate. All the information was contained in an education package. Only one follow up phone call, 6 weeks after the last treatment appointment, was provided by the physical therapist. The purpose of the call was to ask if they had questions about the exercises and encourage compliance. Therefore, both the treatment and control group received no active intervention during or after chemotherapy in order to avoid a possible treatment effect.

### **Data and Statistical Analysis**

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Outcomes for the effect of the treatment and control groups were analyzed with a mixed models analysis, which accounts for repeated measurements, unequal time intervals and data missing at random. Comparisons were made during follow up. Linear mixed models were used to predict continuous outcomes when the assumption of normality was met. Quantile mixed models were used to predict ordinal outcomes or continuous outcomes where the assumption of normality was not met. More than half of the NPRS pain scores were 0 indicating 'no pain'. Due to this floor effect the pain scale score was dichotomized into 0 and 1+ (no pain or pain) for analysis. Logistic mixed models were used for predicting binary outcomes, and the results were marginalized using the approach by Hedeker et al.<sup>27</sup> that converts the 'subject-specific' estimates to 'population-averaged' estimates. Residual plots were used to evaluate the assumption of normality and to detect outliers. The assumption of linearity for continuous predictors was evaluated using restricted cubic splines. The predictors for all models were treatment variable and follow up time. Analyses were run using the R project for statistical computing software version 3.4.1. (R Development team, 2017) and SAS 9.4. Specific programs for the models included; nmle package (linear mixed), lqmm (quantile mixed) and NLMixed (logistic mixed).<sup>28,29</sup>